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$Na_2S_2O_4$ initiated free radical additions of polyfluoroalkyl halides to 4-pentenamides

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Abstract

The free radical additions of fluorine-containing halides to 4-pentenamides initiated by $Na_2S_2O_4$ were investigated. Both polyfluoroalkyl iodide and ethyl iododifluoroacetate, gave rise to fluorine-containing γ-butyrolactones as the main products while bromides such as ethyl bromodifluoroacetate gave the addition–reduction product. After steric and stereo effects on reaction yields were studied using various substrates, it was concluded that the reactions of 4-pentenamides and polyfluoroalkyl iodides provide one alternative approach to prepare γ-butyrolactones with fluorinated side chains.

Keywords: 4-Pentenamide; Fluorine-containing halide; $Na_2S_2O_4$; Free radical addition; γ-Butyrolactones with fluorinated side chain

1. Introduction

Introduction of fluorine into lactones or lactams is of great interest to synthetic chemists due to two facts. First, fluorination of natural products and drugs has demonstrated significant improvements of activities and properties. Second, functionalized lactones or lactams have been found as substructures in a variety of biologically active natural products including flavor components, sex attractant pheromones of different insects, plant-growth regulators, alkaloids, macrocyclic antibiotics, and lignanlactones [1,2]. In previous papers, we reported our results on free radical addition reactions of fluorine-containing iodide to some pentenoic acid derivatives in the presence of $Na_2S_2O_4$ to make fluorine-containing γ-butyrolactones [3–5]. Herein, we extended our research to 4-pentenamide with an expectation of preparing γ-butyrolactams. Surprisingly, fluorine-containing γ-butyrolactones were found to be the main products. The detailed experimental results and analysis were described here.

2. Results and discussion

In the presence of $Na_2S_2O_4$ and sodium bicarbonate, the reaction 3,3-dimethyl-4-pentenamide (**1a**) with iodide **2m** was carried out at room temperature in aqueous acetonitrile solution (CH_3CN:H_2O = 3:1 (v/v)). The reaction was monitored by GC until pentenamide **1a** was consumed completely, followed by workup and evaporation. The purification of the reaction mixture by flash column chromatography afforded a product, whose spectral data indicated that, rather than expected γ-butyrolactam, it was a fluorine-containing γ-butyrolactone **3a**. The same results were obtained when the reactions of other 4-pentenamides bearing different R groups (**1a**–**1f**) with iodides (**2m** and **2n**). And fluorine-containing γ-butyrolactones (**3a**, **3b**, **4a**) were obtained in 40–65% yields (Schemes 1 and 2, Table 1, entries 1–11).

Substituent R^1 of 3,3-dimethyl-4-pentenamide played a significant role on the reaction results. Electron-donating R^1 groups ($R^1 = CH_3$, $C(CH_3)_3$) (Table 1, entries 3–6) led to smooth addition-lactonization reactions occurred while were electron-withdrawing R^1 groups (R^1 = Ph, CH_2Ph) resulted in slow reactions apparently with low yields (Table 1, entries 7–10). Those results suggested that the conjugated effect or large steric hindrance slow down the addition and basic hydrolysis of

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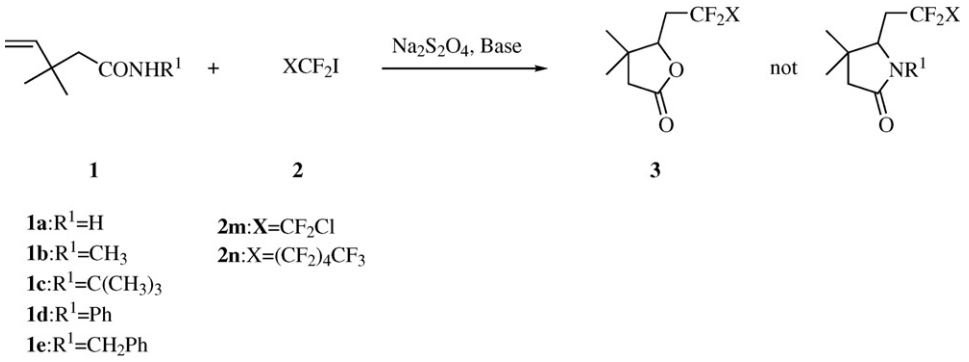
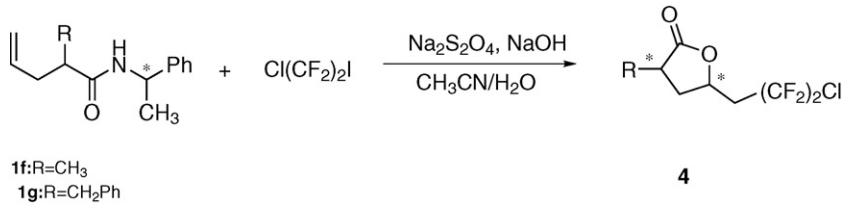


Scheme 1.



Scheme 2.

Table 1
The reactions of 4-pentenamides with XCF_2I

Entry	4-Pentenamide	R_FI	Products/yields (%)[a]
1	**1a**	**2m**	**3a**/50%
2	**1a**	**2n**	**3b**/48%
3	**1b**	**2m**	**3a**/60%
4	**1b**	**2n**	**3b**/59%
5	**1c**	**2m**	**3a**/65%
6	**1c**	**2n**	**3b**/63%
7	**1d**	**2m**	**3a**/45%
8	**1d**	**2n**	**3b**/40%
9	**1e**	**2m**	**3a**/44%
10	**1e**	**2n**	**3b**/40%
11	**1f**	**2m**	**4a**/50%
12	**1g**	**2m**	–[b]

[a] Isolated yields.
[b] No corresponding products.

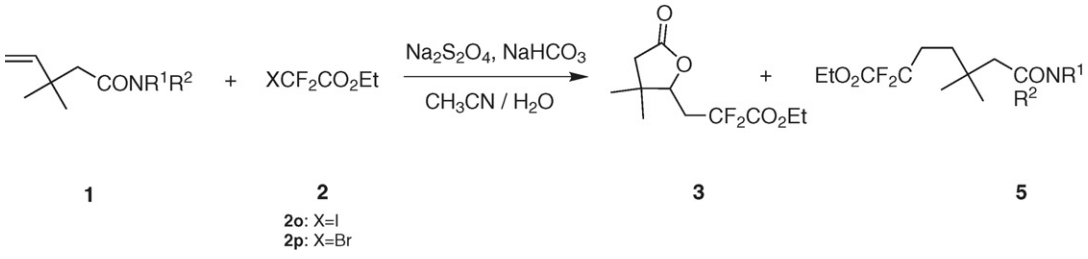
N–Ph or N–CH_2Ph amide. In addition, low solubility of N–Ph or N–CH_2Ph amide in the aqueous acetonitrile solution might contribute to low yields as well.

The reaction was also sensitive to 2-position substitution as well. *N*-(1-phenyl-ethyl)-2-methyl-4-pentenamide (**1f**) and *N*-(1-benzyl-ethyl)-2-benzyl-4-pentenamide (**1g**), were allowed to react with **2m** (Scheme 2). The reaction of 1f proceeded smoothly at room temperature (Table 1, entry 11). In contrast, **1g**, did not give any desired product under the same conditions (Table 1, entry 12).

Further study was focused on how halides effect this reaction (Scheme 3). When ethyl iododifluoroacetate **2o** reacted with **1a** or **1b**, a small quantity of addition-deiodination product was observed along with the main product **3c** (Table 2, entries 1 and 2). While in case of **1c**, **1d**, and **1e**, no reaction occurred (Table 2, entries 3–5). In comparison, when ethyl bromodifluoroacetate **2p** reacted with **1a**, **1b** and **1c**, only the addition–reduction product was isolated (Table 2, entries 6–8). No reaction occurred for **1d** and **1e** (Table 2, entries 9 and 10).

Referring to the literatures [6,7], we proposed lactonization mechanism of the reaction as follows (Scheme 4).

Free radical addition to olefin has been extensively studies while the hydrolysis of the intermediate iodides may undergo two possible pathways. As we know, the hydrolysis of amide is difficult to occur under these mild conditions. The first route was more reasonable than the second. In fact, the reaction of fluorine-containing halides and 4-pentenamides catalyzed by

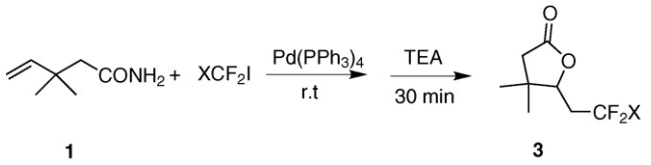


Scheme 3.

Table 2
The reaction of 4-pentenamide with ethyl bromo or iododifluoroacetate

Entry	Amide	X	Compound **3** (%)	Compound **5** (%)[a]
1	**1a**	I	**3c**, 50%	**5a**, minor
2	**1b**	I	**3c**, 49%	**5b**, minor
3	**1c**	I	–[b]	–
4	**1d**	I	–	–
5	**1e**	I	–	–
6	**1a**	Br	–	**5a**, 30%
7	**1b**	Br	–	**5b**, 22%
8	**1c**	Br	–	**5c**, 21%
9	**1d**	Br	–	–
10	**1e**	Br	–	–

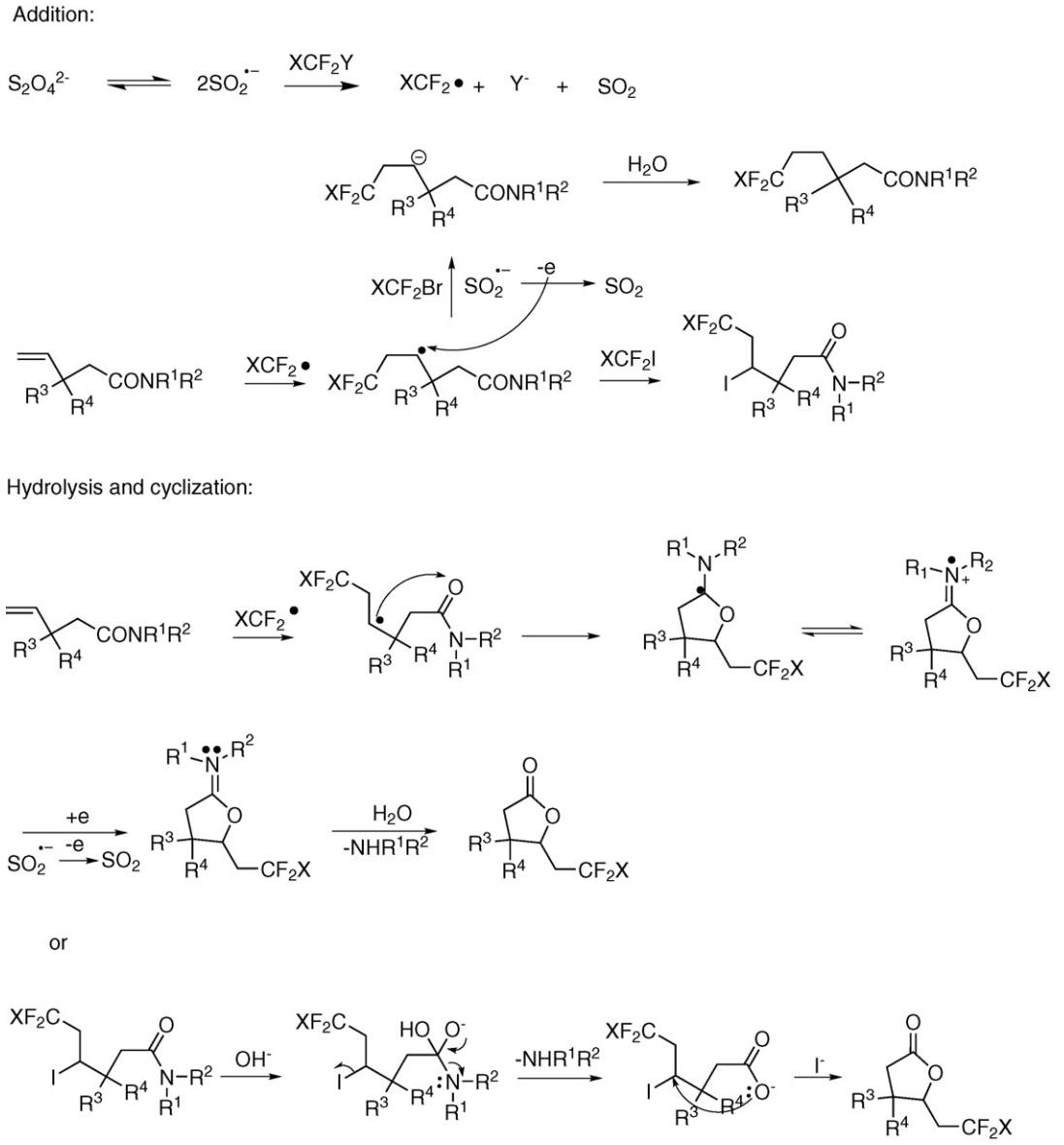
[a] Isolated yields.
[b] (–) indicates no corresponding product is separated.



Scheme 5.

$Pd(PPh_3)_4$ in anhydrous solution proceeded smoothly to give fluorine-containing lactone [8] in high yield after dealing with TEA (Scheme 5, Table 3).

In conclusion, the free radical addition reactions of fluorine-containing halides to 4-pentenamides in the presence of $Na_2S_2O_4$ were investigated. For fluoroalkyl iodides and ethyl iododifluoroacetate, the reaction produced fluorine-containing lactones as the main products instead of fluorine-containing γ-butyrolactams, while only addition–reduction products were separated when ethyl bromodifluoroacetate was used. Various



Scheme 4.

Table 3
The reaction of olefinic amide and fluorine-containing halides catalyzed by $Pd(PPh_3)_4$

Entry[a]	X	Reaction conditions	Products/yield (%)[b]
1	CF_2Cl	rt, 0.5 h	**3a**/90%
2	$(CF_2)_4CF_3$	rt, 0.5 h	**3b**/88%

[a] Reaction conditions: under the protection of N_2, the mixture of olefinic amide (2.5 mmol), XCF_2I (10 mmol), $Pd(PPh_3)_4$ (0.03 mmol) was stirred for 30 min, then plenty of Et_3N was added and stirred for another 30 min.
[b] Isolated yields based on XCF_2I.

4-pentenamides were surveyed and it is apparent that steric as well as electronic effects play the important roles in this reaction; the corresponding mechanism was suggested though the reason why the reaction gave no fluorine-containing γ-butyrolactams was still unclear.

3. Experimental

3.1. General experimental procedures

Melting points were measured on a WRS-1B digital melting point instrument. IR spectra were recorded on a Nicolet FT-IR 20sx IR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were measured on a Bruker AC500 (500 and 125.8 MHz, respectively) spectrometer using TMS as internal standard. ^{19}F NMR spectra were taken on a Bruker AC500 (470.5 MHz) spectrometer; chemical shifts are reported as δ_{CFCl3}, negative for upfield shifts. Mass spectra were obtained on a Finnigan GC–MS 4021 spectrometer. Column chromatography was performed using silica gel H, particle size 10–40 μm.

3.2. Preparation of 4-pentenamide derivatives

3,3-Dimethyl-4-pentenyl chloride (130 mmol) was added drop-wise into a mixture of amine (100 mmol), Et_3N (100 mmol) in 50 mL of solvent at 0 °C, The mixture was stirred at ambient temperature for 10 h. The reaction mixture was acidified with aqueous HCl solution and extracted with ether (3 × 20 mL). Combined organic layers were neutralized with aqueous NaOH solution, washed with saturated brine and dried over anhydrous sodium sulfate. Evaporation of ether followed by recrystallization afforded the desired product.

3.2.1. 3,3-Dimethyl-4-pentenamide (**1a**) [9]

White solid, mp: 73.1–73.7 °C. ^1H NMR ($CDCl_3$) δ: 1.10 (s, 6H, 2 × CH_3), 2.25 (s, 2H, CH_2), 5.00–5.20 (m, 2H, =CH_2), 5.50 (s, broad, 2H, NH_2), 5.80–6.00 (m, 1H, =CH).

3.2.2. N-Methyl-3,3-dimethyl-4-pentenamide (**1b**)

Colorless liquid. ^1H NMR ($CDCl_3$) δ: 1.10 (s, 6H, 2 × CH_3), 2.10 (s, 2H, CH_2), 2.60 (s, 3H, N–CH_3), 4.80–5.00 (m, 2H, CH_2), 5.80–6.00 (m, 1H, CH), 6.10–6.30 (s, broad, 1H, N–H). IR (KBr): 3302, 2962, 1647, 1558, 1411, 911. EI-MS *m/z* (%): 141 (11, M^+), 126 (31, M^+–CH_3), 73 (100), 69 (62), 58 (56), 41 (39). HRMS calcd. for $C_8H_{15}NO$: 141.1154, found: 141.1146.

3.2.3. N-t-Butyl-3,3-dimethyl-4-pentenamide (**1c**)

White solid, mp: 76.4–77.7 °C. ^1H NMR ($CDCl_3$) δ: 1.12 (s, 6H, 2 × CH_3), 1.31 (s, 9H, 3 × CH_3), 2.10 (s, 2H, CH_2), 4.90–5.10 (m, 2H, =CH_2), 5.34 (s, 1H, N–H), 5.80–6.00 (m, 1H, =CH). IR (KBr): 3320, 2964, 1643, 1547. EI-MS *m/z* (%): 183 (31, M^+), 168 (30, M^+–CH_3), 58 (100, $C(CH_3)_3$). HRMS calcd. for $C_{11}H_{21}NO$: 183.1623, found: 183.1631

3.2.4. N-Phenyl-3,3-dimethyl-4-pentenamide (**1d**) [10]

White solid, mp: 101.2–101.6 °C. ^1H NMR ($CDCl_3$) δ: 1.19 (s, 6H, 2 × CH_3), 2.36 (s, 2H, CH_2), 5.10–5.30 (m, 2H, =CH_2), 5.90–6.10 (m, 1H, =CH), 7.09–7.46 (m, 5H, Ph), but no NH peak was observed.

3.2.5. N-Benzyl-3,3-dimethyl-4-pentenamide (**1e**)

Colorless liquid. ^1H NMR ($CDCl_3$) δ: 1.13 (s, 6H, 2 × CH_3), 2.22 (s, 2H, CH_2C=O), 4.41 (d, J = 5.6 Hz, 2H, CH_2Ph), 4.90–5.10 (m, 2H, =CH_2), 5.71–5.81 (s, broad, 1H, N–H), 5.91–6.00 (m, 1H, =CH), 7.27–7.32 (m, 5H, Ph). IR (KBr): 3294, 2962, 1642, 1549, 912, 698. EI-MS *m/z* (%): 217 (15, M^+), 202 (11, M^+–CH_3), 148 (100), 107 (55), 91 (99). HRMS calcd. for $C_{14}H_{19}NO$: 217.1467, found: 217.1475.

3.2.6. N-(1-Phenyl-ethyl)-2-methyl-4-pentenamide (**1f**)

White solid, mp: 77.5–81.0 °C, $[\alpha]_D^{25}$ −77.5 (c 0.01, CH_3COCH_3). ^1H NMR ($CDCl_3$) δ: 1.10–1.25 (m, 3H, CH_3), 1.40–1.50 (m, 3H, CH_3), 2.10–2.25 (m, 2H, CH_2), 2.30–2.50 (m, 1H, CHC=O), 4.90–5.10 (m, 3H, =CH_2 + CHPh), 5.75–5.90 (m, 2H, =CH + NH), 7.25–7.40 (m, 5H, Ph). IR (KBr): 3299, 2967, 1640, 1546, 916, 699. EI-MS *m/z* (%): 217 (12, M^+), 202 (4, M^+–CH_3), 105 (100), 91 (9, CH_2Ph), 77 (13, Ph). HRMS calcd. for $C_{14}H_{19}NO$: 217.1467, found: 217.1458.

3.2.7. N-(1-Phenyl-ethyl)-2-benzyl-4-pentenamide (**1g**)

White solid, mp: 91.5–99.6 °C, $[\alpha]_D^{25}$ −36.5 (c 0.01, CH_3COCH_3). ^1H NMR ($CDCl_3$) δ: 1.18–1.39 (m, 3H, CH_3), 2.28–2.35 (m, 2H, CH_2), 2.47–2.50 (m, 1H, CHCO), 2.77–2.90 (m, 2H, CH_2), 5.00–5.20 (m, 3H, =CH_2 + CHN), 5.20–5.45 (d, J = 57 Hz, 1H, N–H), 5.60–5.80 (m, 1H, =CH), 6.94–7.28 (m, 10H, 2Ph). IR (KBr): 3354 (N–H), 2955, 2877, 1734, 1533, 1235. EI-MS *m/z* (%): 293 (43, M^+), 252 (92), 202 (15, M^+–CH_3–Ph), 148 (59, $CONHCH(CH_3)Ph$), 105 (100), 91 (47), 77 (10). HRMS calcd. for $C_{20}H_{23}NO$: 293.1780, found: 293.1780.

3.3. $Na_2S_2O_4$ initiated radical addition reaction of 4-pentenamide and fluorine-containing halides

Compound **1** (5 mmol) and fluorine-containing halide 2 (6 mmol) were dissolved in a mixture of water (5 mL) and acetonitrile (15 mL). Sodium dithionite (1.0 g) and sodium bicarbonate (0.5 g) were added to the solution portion-wise. The mixture was stirred at ambient temperature. When the reaction was completed, the mixture was treated with water (ca. 30 mL), and extracted with ether (3 × 20 mL). The combined organic layers were washed with saturated brine and dried over anhydrous sodium sulfate. Evaporation of ether followed by column chromatography gave the products **3**, **4** or **5**.

*3.3.1. 5-(3-Chloro-2,2,3,3-tetrafluoro-propyl)-4,4-dimethyl-dihydro-furan-2-one (**3a**) [4]*

Colorless needles, mp: 55–56 °C. ^{1}H NMR ($CDCl_3$) δ: 1.06 (3H, s, CH_3), 1.22 (3H, s, CH_3), 2.25–2.51 (4H, m, 2 × CH_2), 4.32 (1H, d, J = 8.9 Hz, CH). ^{19}F NMR ($CDCl_3$) δ: −71.2 (2F, m, $ClCF_2$), −112.4 (2F, m, CF_2CH).

*3.3.2. 5-(2,2,3,3,4,4,5,5,6,6,7,7,7-Tridecafluoroheptyl)-4,4-dimethyl-dihydro-furan-2-one (**3b**) [4]*

Colorless needles, mp: 52–53 °C. ^{1}H NMR ($CDCl_3$) δ: 1.06 (3H, s, CH_3), 1.22 (3H, s, CH_3), 2.25–2.51 (4H, m, 2 × CH_2), 4.45 (1H, d, J = 9.2 Hz, CH). ^{19}F NMR ($CDCl_3$) δ: −80.7 (3F, m, CF_3), −112.6 (2F, m, CF_2CH_2), −122.7 (2F, m, CF_2), −123.8 (2F, m, CF_2), −124.2 (2F, m, CF_2), −127.1 (2F, m, CF_2).

*3.3.3. 5-(3-Chloro-2,2,3,3-tetrafluoro-propyl)-3-methyl-dihydro-furan-2-one (**4a**) [4,5]*

Oil. ^{1}H NMR ($CDCl_3$) δ: 1.34 (3H, d, J = 7.2 Hz, CH_3), 2.17–2.42 (3H, m, CH_2 + CH), 2.55–2.78 (2H, m, CH_2), 4.80–5.00 (1H, m, CH). ^{19}F NMR ($CDCl_3$) δ: −72.5 (2F, s, $ClCF_2$), −113.7 (2F, m, CF_2CH).

*3.3.4. 2,2-Difluoro-3-(3,3-dimethyl-5-oxo-tetrahydro-furan-2-yl)-propionic acid ethyl ester (**3c**) [4,5]*

Oil. IR: ν_{max}: 2968, 2939, 1781, 1469, 1092 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.05 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.37 (t, J = 7 Hz, 3H, CH_3), 2.26–2.49 (m, 4H, CH_2 + CH_2), 4.31 (d, J = 10 Hz, 1H, CH), 4.37 (q, J = 7 Hz, 2H, CH_2). ^{19}F NMR ($CDCl_3$) δ: −109.45 to −108.91 (m, 1F), −103.00 to −102.44 (m, 1F). EI-MS m/z (%): 250 (M^+, 0.9), 208 (80), 178 (M^+–CO_2Et, 4), 167 (91), 163 (100), 113 (M^+–$CH_2CF_2CO_2Et$). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 175.3, 164.0, 115.3 (m), 81.8, 64.0, 44.4, 40.0, 35.6, 25.1, 21.9, 14.5. HRMS calcd. for $C_{11}H_{16}F_2O_4$ 250.1017, found: 250.1011.

*3.3.5. 6-Carbamoyl-2,2-difluoro-5,5-dimethyl hexanoic acid ethyl ester (**5a**)*

Oil. IR: ν_{max}: 3404, 3200, 2968, 1760, 1660, 1090 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.05 (s, 6H, 2 × CH_3), 1.36 (t, 3H, CH_3, J = 7 Hz), 1.53–1.60 (m, 2H, CH_2), 2.09–2.20 (m, 4H, 2 × CH_2), 4.34–4.50 (q, 2H, OCH_2, J = 7 Hz), 5.30–5.5.0 (s, broad, 1H, NH), 5.50–5.75 (s, broad, 1H, NH). ^{19}F NMR ($CDCl_3$) δ: −107.00 (m, 2F, CF_2). EI: m/z (%): 252 (0.2, M^+), 236 (0.9, M^+–CH_3), 178 (8, M^+–COOEt), 59 (100). HRMS calcd. for $C_{11}H_{19}F_2NO_3$ 252.1411, found: 252.1415.

*3.3.6. N-Methyl-6-carbamoyl-2,2-difluoro-5,5-dimethyl heptanedioic acid ethyl ester (**5b**) [4,5]*

Oil. IR: ν_{max}: 3313, 2960, 1766, 1646, 1556, 1087 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.02 (s, 6H, 2 × CH_3), 1.36 (t, J = 7 Hz, 3H, CH_3), 1.49 (m, 2H, CH_2), 2.03–2.13 (m, 4H, 2 × CH_2), 2.79 (d, J = 4.8 Hz, 3H, N–CH_3), 4.33 (q, J = 7 Hz, 2H, OCH_2), 5.48 (s, 1H, N–H). ^{19}F NMR ($CDCl_3$) δ: −107.1 (m, 2F, CF_2).

*3.3.7. N-t-Butyl-6-carbamoyl-2,2-difluoro-5,5-dimethyl heptanedioic acid ethyl ester (**5c**)*

Oil. IR: ν_{max} 3333, 2964, 1764, 1647, 1542, 1086 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.02 (s, 6H, 2 × CH_3), 1.34–1.37 (m, 12H, 3 × CH_3 + CH_3), 1.49–1.51 (m, 2H, CH_2), 1.95 (s, 2H, CH_2), 2.00–2.05 (m, 2H, CH_2), 4.35 (q, J = 7 Hz, 2H, OCH_2), 5.20–5.30 (s, broad, 1H, N–H). ^{19}F NMR ($CDCl_3$) δ: −106.4 (m, 2F, CF_2). EI-MS m/z (%): 308 (M^+, 0.2), 292 (1), 235(M^+–CO_2Et, 3), 115 (100), 58 (58). HRMS calcd. for $C_{15}H_{27}F_2NO_3$: 307.1959, found: 307.1960.

Acknowledgements

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